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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/526,127
Filing Date: November 06, 2006
Appellant(s): CAMPOCHIARO ET AL.

Dean Nakamura
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 14 January 2011 appealing from the Office action mailed 4/30/2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 4-6, 9-21, 23-26, 28-30, 32-35, 37-39 and 41-48 are cancelled.

Claims 1-3, 27, 31, 36, 40 and 49 are rejected and are under appeal.

Claims 7, 8 and 22 are withdrawn.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The grounds of rejection for review by the Board are whether:

(iv) Claims 1-3, 27, 31 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175);

(v) Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175). as applied to claims 1 and 31 above, and further in view of Poeschla et al. (US-6,555,107); and

(vi) Claims 1-3, 27, 31, 40 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175) in view of Nemerow et al. (US2002/0193327).

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner:

(i) The provisional rejection of claims 1-3, 27, 31 and 36 on the ground of nonstatutory double patenting over claims 1-3, 27-28, 30-32, 38-41, 45, 51-62 of copending Application No. 10/080797 is withdrawn in response to the appellant's abandonment of this application (filed 6/2/2010), thereby rendering the rejection moot.

The appellant notes on page 9 of the Appeal Brief, filed 1/14/2011, "U.S. Patent Application No. 12/785,461 (the '461 application) is a continuation of the '797 application. The claims of the '461 application are essentially the same as those that were pending in the '797 application. Therefore, it might be expected that the rejection on the ground of nonstatutory double patenting would be applied by the Examiner to claims 1-3, 27, 31 and 36 of the present application over claims of the '461 application. On indication of otherwise allowable subject matter, Applicants will consider filing a Terminal Disclaimer over the '461 application if such a rejection were lodged."

As the applicant abandoned Application No. 10/080797 on 6/2/2010, after the instant examiner wrote the Advisory Action, filed 4/21/2010, and the applicant has also indicated that the instant claims could be rejected by the Examiner over the claims of Application No. 12/785,461, the examiner could introduce a provisional ODP rejection over the claims of Application No. 12/785,461.

(ii) The provisional rejection of claims 1 and 31 on the ground of nonstatutory double patenting over claims 52-56, and 59 of copending Application No. 10/910293 is withdrawn in response to the appellant's abandonment of this application, thereby rendering the rejection moot.

(iii) The rejection of claims 1, 31, 36 and 40 under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) and further in view of Brandt et al. (US-6106826) is withdrawn in response to the appellant's arguments.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Rasmussen et al. (*Drug Discovery Today*. 22 November 2001; 6(20): 1171-1175)

http://diabetes.webmd.com/tc/diabetic-retinopathy-what-happens (2011)

USPAT-6,555,107	POESCHLA ET AL	04-2003
US2002/0193327	NEMEROW ET AL	12-2002
US2010/0286253	BRAZZELL ET AL	11-2010

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rasmussen

Claims 1-3, 27, 31 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175).

Claim 1 is directed to a method for the treatment of retinal edema in an individual afflicted with retinal edema, comprising effecting an increase in the amount of endostatin in ocular tissues of an individual afflicted with retinal edema to a retinal edema-inhibiting effective amount, wherein the increase is effected by a subretinal injection of an effective amount of a replication-defective viral vector comprising an endostatin-encoding nucleic acid to the individual.

Rasmussen et al. is a review article which teaches "anti-angiogenic gene therapies for disorders of the eye" (title). *Rasmussen et al.* teach "In pDR [proliferative diabetic retinopathy], the diabetic microangiopathy...results in...angiogenic stimulation...[t]his leads to the ingrowth of new vessels from the retina and the optic nerve. Bleeding and leakage with subsequent scarring, as well as retinal detachment...the development of macular edema" (page 1171, col.2, lines 12-22). Therefore, Rasmussen et al. teach that one symptom of diabetic retinopathy is macular edema, caused by neovascularization of the retina, thereby suggesting a nexus between retinal neovascularization in diabetic retinopathy and macular edema.

Rasmussen et al. teach "A gene therapy approach, using a replication-deficient viral vector to carry the gene encoding the anti-angiogenic substance represents one potential solution to this problem.....administered by intravitreal or subretinal injection is highly effective in preventing neovascularization (page 1174, *Conclusion* Section, col.1 bridging col.2, emphasis added by examiner), thereby suggest limitations of claim 1 directed to: "subretinal injection of...a replication-defective viral vector comprising" an antiangiogenic protein. Rasmussen teach gene therapy methods using recombinant viral vectors to carry the gene encoding pigment epithelium-derived factor (PEDF) or endostatin (page 1172, col.2, Anti-angiogenic gene therapy section), thereby suggesting the limitations of claim 1 directed to "viral vectors comprising an endostatin-encoding nucleic acid."

Rasmussen further teaches that lentivirus (HIV) gene delivery systems can be used to delivery therapeutic proteins to the posterior part of the eye (page 1172, col.1,

Gene transfer section). Rasmussen also teach that a "replication deficient adenovirus vector" can be used to deliver genes encoding anti-angiogenic proteins to the retina (page 1173, col.2, *Gene therapy with PEDF (AdPEDF)* section). Rasmussen specifically teach "subretinal injection is highly effective in preventing neovascularization" (page 1174, col.2, lines 10-11), thereby providing motivation for using subretinal injection.

Macular edema is swelling of the retina caused by leakage from blood vessels in the eye (WebMD). Furthermore, Rasmussen teach that proliferative diabetic retinopathy (pDR) is one of the diseases which can be treated by the methods described within the review article. Additionally, Rasmussen et al. specifically teach that methods of ocular gene therapy can be used to treat diabetic retinopathy, of which one of the symptoms is retinal edema.

The preamble of the instant claim recites "treatment of retinal edema in an individual afflicted with retinal edema" but does not explicitly recite treating a specific disease. In fact, the applicant only uses the word, "disease," two times in his application. Within the instant specification, there are numerous references to "an individual afflicted with a retinal disorder." The instant specification also states, "[r]etinal disorders include, e.g., retinal detachment and retinal edema, including macular edema" (page 2, lines 13-14). However, retinal edema does not exist by itself; rather, it is a symptom of diseases such as proliferative diabetic retinopathy. Furthermore, the applicant does not specify disease populations which encompass "an individual afflicted with retinal edema." Given the silence of the instant specification regarding diseases

associated with retinal edema, a skilled artisan necessarily looks to general knowledge in the field of medicine, regarding macular edema. As an indication of knowledge in the art, WebMD indicates that "swelling and distortion of the macula (macular edema), which results from buildup of fluid, is the most common complication of retinopathy" (http://diabetes.webmd.com/tc/diabetic-retinopathy-what-happens). Therefore, the Office concludes that a skilled artisan would recognize that applying a gene therapy method of treating proliferative diabetic retinopathy by subretinal injection of an endostatin-encoding nucleic acid to an individual having the symptoms of proliferative Diabetic Retinopathy (specifically, neovascularization and its consequential fluid leakage from the newly formed blood vessels in the macula) encompasses "a method for the treatment of retinal edema in an individual afflicted with retinal edema." In other words, proliferative diabetic retinopathy (exhibiting neovascularization) is a disease wherein individuals are afflicted with retinal edema.

Rasmussen provides teaching, suggestion, motivation and specific scientific rationale for the practicing the claimed invention:

> Ocular neovascularization is a key factor of the most common causes of blindness in humans in the developed world: age-related macular degeneration and proliferative diabetic retinopathy. Prevention of ocular neovascularization by deployment of anti-angiogenic drugs represents a rational and appealing therapeutic approach. However, because these are chronic diseases characterized by ongoing new vessel formation, long-term inhibition of the angiogenic stimuli is likely to be needed....A gene therapy approach, using a replication-deficient viral vector to carry the gene encoding the anti-angiogenic substance represents one potential solution to this problem. (page 1174, *Conclusion* Section, col.1 bridging col.2, emphasis added by examiner).

Therefore, a skilled artisan reading Rasmussen would understand that using antiangiogenic gene therapy methods to treat the cause of macular edema, namely the

formation of new blood vessels in the retina, was envisioned prior to the instant application. The fact that Rasmussen describes the causes of macular edema as being related to angiogenesis, guides a skilled artisan to interpret the remaining portions of the Rasmussen review article as being relevant for treating macular edema through antiangiogenic gene therapy methods. With a skilled artisan's understanding of the causes of macular edema in diabetic retinopathy, the context of anti-angiogenic gene therapy for the retina as taught throughout Rasmussen is obvious for treating the symptoms of diabetic retinopathy, namely (macular) retinal edema.

Claims 2, 3 and 27 are directed to the human endostatin polypeptide sequence of SEQ ID NO:1 (claim 2), fragments of SEQ ID NO:1 (claim 3), and the human endostatin polynucleotide sequence SEQ ID NO:2 (claim 27). The human endostatin sequence has been highly studied and is known to a skilled artisan. Furthermore, fragments of endostatin having anti-angiogenic activity are well known to a skilled artisan. Accordingly, a skilled artisan in the possession of Rasmussen would be able to utilize the claimed sequences.

Claim 31 is directed to the method of claim 1, wherein the viral vector is a lentiviral vector. Rasmussen et al teach lentivirus vectors for delivery of anti-angiogenic genes (page 1172, col.1, Gene transfer section).

Claim 49 is directed to the method of claim 1, wherein the viral vector is a retroviral vector. The lentivirus, HIV, is a retrovirus.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to practice a method of treating retinal edema in an individual

comprising subretinal injection of an effective amount of a replication-defective lentiviral vector comprising an endostatin-encoding nucleic acid to the individual.

The person of ordinary skill in the art would have been motivated to practice this method, because Rasmussen teaches a gene method for treating macular edema by administering viral vectors encoding endostatin to a patient.

Furthermore, Rasmussen suggests that lentivirus vectors are a suitable vector for such methods and that subretinal injection is also suitable for such treatments.

Additionally, Rasmussen specifically suggests, "a gene therapy approach, using a replication-deficient viral vector to carry the gene encoding the anti-angiogenic substance represents one potential solution to this problem" (page 1174, col.1 bridging col.2), thereby providing motivation for the practicing a method with a replication-defective viral vector.

Rasmussen specifically teach "subretinal injection is highly effective in preventing neovascularization" (page 1174, col.2, lines 10-11), thereby providing motivation for using subretinal injection.

Rasmussen et al teach, "Prevention of ocular neovascularization by deployment of [gene therapy] anti-angiogenic drugs" to treat diabetic retinopathy (page 1174, *Conclusion* Section, col.1 bridging col.2) and *Rasmussen et al.* also teach "In pDR, the diabetic microangiopathy...results in...angiogenic stimulation...[t]his leads to the ingrowth of new vessels from the retina and the optic nerve. Bleeding and leakage with subsequent scarring, as well as retinal detachment...the development of macular

edema" (page 1171, col.2, lines 12-22), thereby suggesting motivation for treating the cause of retinal edema in diabetic retinopathy, namely neovascularization.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods comprising administering the human endostatin gene for treating the cause of retinal edema, gene therapy methods comprising a replication-defective viral vectors for ocular gene therapy, and subretinal injection) are taught by Rasmussen and further they are taught in various combinations and are shown to be used in gene therapy methods for treating diabetic retinopathy. It would be therefore predictably obvious to use a combination of these elements in a method of gene therapy for retinal edema.

An artisan would have expected success in practicing the method suggested by Rasmussen. Rasmussen is a review article describing many overlapping methods for treating retinal neovascularization in diseases such a proliferative diabetic neuropathy, which demonstrates the symptoms of retinal edema as a result of neovascularization. Therefore, there was some success in this field prior to the filing of the instant application. Accordingly, there is ample reason to believe that practicing the active methods steps suggested by Rasmussen would be successful.

Therefore the method as taught by Rasmussen et al would have been *prima facie* obvious over the method of the instant application.

Rasmussen & Peoschla

Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175). as applied to claims 1 and 31 above, and further in view of Poeschla et al. (US-6,555,107).

The teachings of claims 1 and 31 are described above in the obviousness rejection over Rasmussen.

In summary, Rasmussen suggests gene therapy methods for treating macular edema by subretinal injection of replication-defective lentiviral vectors comprising a polynucleotide encoding endostatin.

Although Rasmussen et al. teaches using lentiviral vectors, they do not teach the particular species of lentivirus vector, Bovine Immunodeficiency Virus (BIV).

However, Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34). In addition, Poeschla et al teach methods of gene therapy comprising infecting a cell of the eye with a non-primate lentivirus capable of expressing a heterologous gene (col.33, line 6). Furthermore, Poeschla et al. teach methods of administration comprising injection.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Rasmussen et al. and Poeschla et al.

to treat retinal edema using lentiviral vectors such as Bovine Immunodeficiency Virus (BIV) comprising the gene for human endostatin. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods comprising administering the human endostatin gene for treating retinal edema and gene therapy methods comprising a BIV delivery vector) are taught by Rasmussen or Poeschla and further they are taught in various combinations and are shown to be used in gene therapy methods for the eye. It would be therefore predictably obvious to use a combination of these elements in a method of gene therapy for retinal edema.

The person of ordinary skill in the art would have been motivated to make those modifications because Poeschla et al teach non-primate lentivirus vectors, including BIV, are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34). In addition, subretinal and intravitreal injections were known in the art of treating retinal diseases.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Rasmussen et al. and Poeschla et al. because the cited art provides examples of successful gene delivery by lentiviruses.

Therefore the method as taught by Rasmussen et al in view of Poeschla et al. would have been *prima facie* obvious over the method of the instant application.

Rasmussen & Nemerow

Claims 1-3, 27, 31, 40 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175) in view of Nemerow et al. (US2002/0193327).

The teachings of Rasmussen are described above in the obviousness rejection over Rasmussen.

In summary, Rasmussen suggests gene therapy methods for treating macular edema by subretinal injection of replication-defective lentiviral vectors comprising a nucleic acid encoding endostatin.

Rasmussen et al. does not teach using inducible promoters in their viral vectors.

Claim 40 is directed to the method of claim 1, wherein the increase is inducibly effected by the administration to the individual of a viral vector that can cause the production in the individual of an agent that will induce the expression of the endostatin-encoding nucleic acid. Nemerow et al. suggest gene therapy methods of treating retinal diseases (abstract) including macular edema (Table 4, page 15) comprising subretinal injection (parag.0024) of viral vectors having inducible promoters (parag.0060) operably linked to a therapeutic gene. Furthermore, Nemerow teaches that endostatin can inhibit angiogenesis (parag.0165).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Rasmussen et al. and Nemerow et al.

to treat retinal edema by subretinal injection of a lentiviral vector comprising the gene for human endostatin operably linked to an inducible promoter.

The person of ordinary skill in the art would have been motivated to utilize inducible promoters for expression of endostatin in gene therapy methods of treating retinal edema. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods comprising administering the human endostatin gene for treating retinal edema, gene therapy methods comprising a lentivirus vector, and using inducible promoter for ocular gene therapy) are taught by Rasmussen or Nemerow and further they are taught in various combinations and are shown to be used in gene therapy methods for the eye. It would be therefore predictably obvious to use a combination of these elements in a method of gene therapy for retinal edema. In addition, in the art of gene therapy, it a desired goal to control the time and location of gene expression; inducible promoters provide control over these parameters.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Rasmussen et al. and Nemerow et al. because inducible promoters have been used successfully in gene therapy methods.

Therefore the method as taught by Rasmussen et al in view of Nemerow et al. would have been *prima facie* obvious over the method of the instant application.

(10) Response to Argument

Rasmussen

Claims 1-3, 27, 31 and 49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175) for the reasons of record and the comments below.

The appellant's arguments have been fully considered but are unpersuasive.

The appellant makes two specific arguments:

(i) *Rasmussen do not teach the use of endostatin for treating retinal edema.*

The appellant argues "the mention of macular edema in Rasmussen is in the 'Introduction' section and Applicants were unable to find 'edema' mentioned anywhere else in Rasmussen" (Brief, filed 1/24/2011, page 18) and "Rasmussen et al. reference is limited to discussing anti-angiogenic therapies and does not teach treating edema" (Brief, filed 1/24/2011, page 18).

Rasmussen et al. teach "In pDR [proliferative diabetic retinopathy], the diabetic microangiopathy...results in...angiogenic stimulation...[t]his leads to the ingrowth of new vessels from the retina and the optic nerve. Bleeding and leakage with subsequent scarring, as well as retinal detachment...the development of macular edema" (page 1171, col.2, lines 12-22). Therefore, Rasmussen et al. teach that one symptom of diabetic retinopathy is macular edema, caused by neovascularization of the retina.

The preamble of the instant claim recites "treatment of retinal edema in an individual afflicted with retinal edema" but does not explicitly recite treating a specific disease. In fact, the applicant only uses the word, "disease," two times in his application. Within the instant specification, there are numerous references to "an individual afflicted with a retinal disorder." The instant specification also states, "[r]etinal disorders include, e.g., retinal detachment and retinal edema, including macular edema" (page 2, lines 13-14). However, retinal edema does not exist by itself; rather, it is a symptom of diseases such as proliferative diabetic retinopathy. Furthermore, the applicant does not specify disease populations which encompass "an individual afflicted with retinal edema." Given the silence of the instant specification regarding diseases associated with retinal edema, a skilled artisan necessarily looks to general knowledge in the field of medicine, regarding macular edema. As a showing of fact for the Board, WebMD indicates that "swelling and distortion of the macula (macular edema), which results from buildup of fluid, is the most common complication of retinopathy" (http://diabetes.webmd.com/tc/diabetic-retinopathy-what-happens). Therefore, the Office concludes that a skilled artisan would recognize that applying a gene therapy method of treating proliferative diabetic retinopathy by subretinal injection of an endostatin-encoding nucleic acid to an individual having the symptoms of pDR (specifically, neovascularization and its consequential fluid leakage from the newly formed blood vessels in the macula) encompasses "a method for the treatment of retinal edema in an individual afflicted with retinal edema." In other words, proliferative

diabetic retinopathy (exhibiting neovascularization) is a disease wherein individuals are afflicted with retinal edema.

Rasmussen provides teaching, suggestion, motivation and specific scientific rationale for the practicing the claimed invention:

> Ocular neovascularization is a key factor of the most common causes of blindness in humans in the developed world: age-related macular degeneration and proliferative diabetic retinopathy. Prevention of ocular neovascularization by deployment of anti-angiogenic drugs represents a rational and appealing therapeutic approach. However, because these are chronic diseases characterized by ongoing new vessel formation, long-term inhibition of the angiogenic stimuli is likely to be needed....A gene therapy approach, using a replication-deficient viral vector to carry the gene encoding the anti-angiogenic substance represents one potential solution to this problem. (page 1174, *Conclusion* Section, col.1 bridging col.2).

Therefore, a skilled artisan reading Rasmussen would understand that using antiangiogenic gene therapy methods to treat the cause of macular edema, namely the formation of new blood vessels in the retina, was envisioned prior to the instant application. The fact that Rasmussen describes macular edema as being induced by abnormal angiogenesis, guides a skilled artisan to interpret the remaining portions of the Rasmussen review article as being relevant for treating macular edema through antiangiogenic gene therapy methods. Accordingly, the Office is unpersuaded by the appellant's remarks regarding the paucity of occurrences of the word, "edema," in Rasmussen by which the appellant suggests Rasmussen is deficient in providing guidance for the limitations of the instant claims. Rather, with a skilled artisan's understanding of the causes of macular edema in diabetic retinopathy, the context of anti-angiogenic gene therapy for the retina is obvious in the field of treating the symptoms of diabetic retinopathy, namely (macular) retinal edema.

(ii) *Brandt provides a teaching away from the claimed method and this should be considered when determining a prima facie case of obviousness over Rasmussen.* It is noted that the present rejection does not rely on Brandt et al. However, the appellant has argued that such a reference indicates that the art teaches away from the presently claimed invention.

Rasmussen provides explicit teaching, suggestion, motivation and specific scientific rationale for the practicing the claimed invention:

> Ocular neovascularization is a key factor of the most common causes of blindness in humans in the developed world: age-related macular degeneration and proliferative diabetic retinopathy. Prevention of ocular neovascularization by deployment of anti-angiogenic drugs represents a rational and appealing therapeutic approach. However, because these are chronic diseases characterized by ongoing new vessel formation, long-term inhibition of the angiogenic stimuli is likely to be needed....A gene therapy approach, using a replication-deficient viral vector to carry the gene encoding the anti-angiogenic substance represents one potential solution to this problem.....administered by intravitreal or subretinal injection is highly effective in preventing neovascularization (page 1174, *Conclusion* Section, col.1 bridging col.2, emphasis added by examiner).

Rasmussen (issued 22 November 2001) provide explicit motivation for subretinal injection of replication-deficient viral vectors encoding anti-angiogenic proteins. Furthermore, one of the main topics discussed in the Rasmussen review article is preventing the causes of the symptoms (e.g., macular edema) of proliferative diabetic retinopathy by inhibition of neovascularization with endostatin gene therapy. Rasmussen et al. specifically teach that macular edema is a symptom of proliferative diabetic retinopathy (pDR) (page 1171, col.2, line 22).

Brandt (US-6,106,826; filed 17 Dec 1997 and issued 22 August 2000) promotes replication competent avirulent Herpes Simplex Virus vectors for retinal gene therapy

(col.14, claim 1). This is interpreted by the appellant as teaching away from the claimed invention, requiring "a replication-defective viral vector." The Office notes that the field of gene therapy has explored a variety of viral and non-viral vectors during its relatively brief history. Many researchers choose to focus on a particular vector type and devote their efforts to maximizing its potential. The examiner interprets both Brandt and Rasmussen as promoting their particular view of a "best" vector. As indicated above, Rasmussen provides specific teaching, suggestion and motivation to utilize a method obvious over the instant claims: "because these are chronic diseases characterized by ongoing new vessel formation, long-term inhibition of the angiogenic stimuli is likely to be needed....A gene therapy approach, using a replication-deficient viral vector to carry the gene encoding the anti-angiogenic substance represents one potential solution to this problem.....administered by intravitreal or subretinal injection is highly effective in preventing neovascularization (page 1174, *Conclusion* Section, col.1 bridging col.2, emphasis added by examiner). Rasmussen, having published their review article after the issuance of Brandt, was presumably aware of Brandt's teachings, but nevertheless guides the skilled artisan to use replication-deficient viral vectors. Therefore, the Office, having considered the teachings of Brandt and Rasmussen continue to find that Rasmussen guide skilled artisan to use replication-deficient viral vectors. Therefore, the examiner finds the appellant's argument unpersuasive.

The appellant further suggests that methods for inhibiting retinal edema by inhibiting neovascularization was not understood prior to the instant invention (Brief, page 19, lines 1-4). The examiner finds this argument unpersuasive, because

Rasmussen, though not as succinctly, as the examiner's prior sentence or the appellant's words (Brief, page 19, lines 1-4), guides a skilled artisan to practice a method for inhibiting retinal edema by inhibiting neovascularization. As elaborated above, a skilled artisan knew at the time of the instant invention, that "swelling and distortion of the macula (macular edema), which results from buildup of fluid, is the most common complication of retinopathy" (http://diabetes.webmd.com/tc/diabetic-retinopathy-what-happens). Rasmussen provides these same teachings: "In pDR [proliferative diabetic retinopathy], the diabetic microangiopathy...results in...angiogenic stimulation...[t]his leads to the ingrowth of new vessels from the retina and the optic nerve. Bleeding and leakage with subsequent scarring, as well as retinal detachment...the development of macular edema" (page 1171, col.2, lines 12-22). In this way, Rasmussen guides the skilled artisan to inhibit angiogenesis and then proceeds to review the relevant art which has applied antiangiogenic gene therapy for treating neovascularization in diabetic retinopathy. In conclusion, Rasmussen provides specific teaching, suggestion and motivation to practice the steps of the instantly claimed invention: "because these are chronic diseases characterized by ongoing new vessel formation, long-term inhibition of the angiogenic stimuli is likely to be needed....A gene therapy approach, using a replication-deficient viral vector to carry the gene encoding the anti-angiogenic substance represents one potential solution to this problem.....administered by intravitreal or subretinal injection is highly effective in preventing neovascularization (page 1174, *Conclusion* Section, col.1 bridging col.2,

emphasis added by examiner). Accordingly, the Office finds the appellant's argument unpersuasive.

Under the arguments directed to the withdrawn rejection of claims 1, 31, 36 and 40 under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) and further in view of Brandt et al. (US-6106826), the appellant states "Brandt et al. describe replication defective viral vectors as being problematic with serious limitations, particularly in the area of ocular delivery (Brandt et al., column 3, lines 49-57)" (Brief, page 10, lines 6-9). As noted above, the examiner views these teachings are merely being advocacy for Brandt's particular invention. It is well known in the art of gene therapy that all kinds of vectors have been used for a variety of conditions. Contrary to Brandt, Rasmussen clearly advocates for using "replication-deficient viral vectors" for ocular delivery. Therefore, taking the art as a whole, the Brandt referece is insufficient to overcome the explicit guidance provided by Rasmussen for "replication-deficient viral vectors." Accordingly, the Office finds the appellant's argument unpersuasive.

Under the arguments directed to the withdrawn rejection of claims 1, 31, 36 and 40 under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) and further in view of Brandt et al. (US-6106826), the appellant states "Brandt et al. teach that subretinal injection causes retinal detachment. One skilled in the art at the time of invention would have wanted to avoid retinal detachment or further retinal detachment when treating retinal edema" (Brief, page 10, lines 11-13). Rasmussen explicitly teaches motivation for using

subretinal injection of replication deficient viral vectors: "Preclinical studies in models of retinal neovascularization...have demonstrated that AdPEDF, administered by intravitreal or subretinal injection is highly effective in preventing neovascularization" (page 1174, col.2, lines 5-7, emphasis added by examiner). Rasmussen clearly advocates for using "subretinal injection of replication-deficient viral vectors" for ocular delivery of polynucleotides encoding antiangiogenic molecules. Therefore, the examiner does not deem the particularly cited teachings of Brandt as being sufficient to overcome the explicit guidance provided by Rasmussen for "subretinal injection of replication-deficient viral vectors." Rasmussen and knowledge of one skilled in the art indicate that retinal detachment (due to neovascularization) is a symptom of diabetic retinopathy (Rasmussen page 1171, col.2, lines 6 and 20). Rasmussen and knowledge of a skilled artisan suggest reduction of bleeding and leakage in the retina due to neovascularization (i.e., retinal edema), the cause of retinal detachment in diabetic neuropathy, can be accomplished by administering anti-angiogenic molecules. All the art reviewed by Rasmussen indicates that subretinal injection is effective for treating retinal detachment. There is no art cited by Rasmussen's review which indicates otherwise. Therefore, taking the art as a whole, the Brandt reference is insufficient to overcome the explicit guidance provided by Rasmussen for subretinal injection delivery of antiangiogenic molecule for the treatment of macular edema. Therefore, the Office finds the appellant's argument unpersuasive.

The appellant also argues "one skilled in the art would not have had a reasonable expectation of successfully practicing the claimed invention" (Brief, page 19,

parag.2). Rasmussen is a review article describing many overlapping methods for treating retinal neovascularization in diseases such a diabetic neuropathy, which demonstrate the symptoms of retinal edema as a result of neovascularization. Therefore, there was some success in this field prior to the filing of the instant application. Accordingly, there is ample reason to believe that practicing the active methods steps suggested by Rasmussen, (which is almost verbatim the claimed invention,) would be successful. Accordingly, the Office finds the appellant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1-3, 27, 31 and 49 under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175).

Rasmussen & Poeschla

Claim 36 remains rejected under 35 U.S.C. 103(a) as being as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175). as applied to claims 1 and 31 above, and further in view of Poeschla et al. (US-6,555,107) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant argues that despite teaching "Bovine Immunodeficiency Virus (BIV)," Poeschla "does not cure the other fatal deficiencies of Rasmussen et al. as to the claimed invention, as discussed in Section VII.B.ii, pages 18 and 19 above" (Brief, page 19, section iii). Therefore, the applicant has provided no additional arguments

which were not addressed in the discussion of Rasmussen above. Accordingly, the Office finds the appellant's arguments unpersuasive.

Therefore, the examiner hereby maintains the rejection of claim 36 under 35 U.S.C. 103(a) as being as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175). as applied to claims 1 and 31 above, and further in view of Poeschla et al. (US-6,555,107).

Rasmussen & Nemerow

Claims 1-3, 27, 31, 40 and 49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175) in view of Nemerow et al. (US2002/0193327) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant argues that despite teaching "inducible promoters," Nemerow "does not cure the other fatal deficiencies of Rasmussen et al. as to the claimed invention, as discussed in Section VII.B.ii, pages 18 and 19 above" (Brief, page 20, section iv). Therefore, the applicant has provided no additional arguments which were not addressed in the discussion of Rasmussen above. Accordingly, the Office finds the appellant's arguments unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1-3, 27, 31, 40 and 49 under 35 U.S.C. 103(a) as being as being unpatentable over Rasmussen et al.

(Drug Discovery Today. 22 November 2001; 6(20): 1171-1175) in view of Nemerow et al. (US2002/0193327).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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